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Accessibility and Inclusivity of Chimeric Antigen Receptor T-cell Immunotherapy in Treating Hematological Malignancies

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Authors' contributions

This work was carried out in collaboration among all authors. All authors conducted this research collaboratively, and collectively bear full responsibility for its content. We recognize that all the writers included in this paper made significant contributions to the effective conclusion of the study. Author OMA is accountable for the creation and coordination of this work. Author FAU was responsible for editing, proofreading, and organizing the references. Authors FAU, CBA, AO and OMA developed the manuscript. Authors OBO participated in searching for research papers used in writing this review. Author KEAU proofread the paper before the final submission. All authors thoroughly reviewed the paper, provided vital contributions, and approved the final version to be published. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Targeting the molecule cluster of differentiation 19 (CD19), chimeric antigen receptor (CAR)-T-cell therapy is an artificial immune cell therapy now used in clinical practice for hematological malignancies.

Studies on CAR-T-cell therapy have shown that it is highly effective, with high objective response rates (ORRs) and, in certain cases, promising progression-free survival (PFS). Notwithstanding, impediments can arise because of the emergence of resistance mechanisms, including the loss of CD19 antigen and immune suppression caused by the tumor microenvironment. Immune checkpoint inhibitors, allogeneic CAR-T cell treatment, and sequential CAR-T cell therapy are methods employed to overcome these barriers. Research on the use of CAR-T-cell therapy for T-cell malignancies and other disorders is still underway, despite the treatment's impressive results in treating B-cell malignancies. The therapy's high purchase cost and the lack of conclusive clinical proof make cost-effectiveness difficult to achieve. The scarcity of specialist facilities providing CAR-T therapy further impedes access, necessitating patients to surmount logistical and financial obstacles. To increase accessibility and affordability and to ascertain its long-term cost-effectiveness, more thorough investigations are required. CAR T-cell immunotherapy has a bright future ahead of it but to be used more widely and fairly, several important issues must be resolved. This review paper aims to assess critically the current accessibility and inclusivity of CAR T cell immunotherapy, identifying barriers and opportunities to enhance its application in the treatment of hematological malignancies.

Keywords: CAR T cells; immunotherapy; hematological malignancies; Accessibility and equity in immunotherapy; cancer treatment; Chimeric Antigen Receptor; CD19 Antigen; CAR T cell Immunotherapy; Allogenic CAR-T cells; Immune checkpoint inhibitors; CAR-T cell cost-effectiveness.

1. INTRODUCTION

Chimeric antigen receptor (CAR) T-cell therapy is a cancer treatment that modifies a patient's T cells in the lab, equipping them to attack cancer cells more effectively. Sometimes, it is considered as a form of gene therapy, as it involves altering the T cells' genetic makeup. CAR T-cell therapy is often used when other treatments are no longer effective and has shown great promise in treating certain types of cancer [1,2]. The type of cancer mostly treated using this form of immunotherapy is hematological malignancies [3]. Although this treatment has shown promise, more research needs to be done to address areas of toxicity or adverse effects, efficacy, and cost-effectiveness of this treatment. The purpose of this review is to explore the clinical application and accessibility of CAR T-cell therapy especially for the under-represented minority groups and other marginalized communities that may not be able to undergo this treatment.

2. CLINICAL APPLICATION OF CAR T-CELL IN THE TREATMENT OF HEMATOLOGICAL MALIGNANCIES

2.1 Car-T Cell Therapy in Acute Lymphoblastic Leukemia (ALL)

Treating patients with ALL, particularly those with r/r B-ALL (a form of the disease that's resistant to treatment and often deadly), is where CAR-T

therapy is the most suitable treatment. In the treatment of ALL, anti-CD19 CARs, which target a biomarker commonly found in B-ALL, have been the most effective. Other potential targets include anti-CD20 and immunoglobulin light chains. The first-generation CARs, which only contained CD3ζ chains, were not very effective and had a short lifespan in the body [4,5]. This led to the development of second-generation CARs, which combined CD28 or 4-1BB with CD3ζ. Clinical trials using CD19-targeted CAR-T cells in adults and children with relapsed or refractory B-ALL have shown high rates of complete and partial remission. In one study, after conditioning therapy, T cells were infused, and 15 out of 16 patients received the necessary amount of T cells. The complete remission rate was an impressive 88%, implying that the complete remission was of high quality, with very few detectable disease indicators detected by advanced molecular assays [6].

2.2 Car-T Cell Therapy in Chronic Lymphocytic Leukemia (CLL)

CLL is a type of cancer that varies in its clinical course and response to chemotherapy, and stem-cell transplantation is the only cure [7]. CD19 CAR-T cells have shown promise in treating patients with relapsed and high-risk CLL, with equal rates of complete and partial remission. Researchers are also exploring other targets, like the trans-membrane receptor, for possible CAR-T cell treatments for CLL [8]. More excitingly, research suggests that CAR-T cells can even be used to treat patients who experience a relapse of B-cell malignancies after a stem cell transplant from a donor (allogeneic hematopoietic stem cell transplant or allo-HSCT). Traditionally, researchers use donor lymphocyte infusions to treat B-cell malignancies after allo-HSCT but these infusions can cause a terrible side effect called graft-versus-host disease (GVHD) that affects about a third of patients and is a leading cause of death from donor lymphocyte infusions [6].

2.3 Car-T Cell Therapy in Lymphoma

For patients with lymphoma who have failed multiple rounds of treatment, the prognosis can be poor even with improved chemotherapy and monoclonal antibody therapies. However, CAR-T cells provide a promising new treatment option for patients who have not responded to multiple rounds of chemotherapy and have emerged as a cutting-edge immunotherapy for relapsed or chemotherapy-resistant B-cell non-Hodgkin lymphoma (NHL) [9]. Different types of CARs have been developed to modify T cells, with the anti-CD19 CAR-T cell being one of the earliest and most well-known. In lymphoma treatment, first-generation CAR-T cells failed to perform as well as later generations in terms of controlling tumor growth and longevity.

Studies have shown that second- and third-generation CAR-T cells, which use either CD28 or 4-1BB cytoplasmic signaling domains, are better at expanding and fighting tumors, both in lab experiments and in living animals. CD28 is effective in boosting cell growth and survival while 4-1BB is particularly good at promoting anti-tumor activity in certain types of B-cell malignancies [6].

2.4 Car-T in Multiple Myeloma

Multiple myeloma (MM) is a cancer that is difficult to treat because it starts in the bone marrow, and despite chemotherapy, stem cell transplants, and immune-modulating drugs, it remains uncured. However, there is some hope because it has been observed that MM can be put into remission through a graft-versus-myeloma effect in stem cell transplants, which shows the potential of T-cell-based immunotherapy as a possible treatment option [10]. Myeloma cells do not express CD19 as often as other cancer cells do, so anti-CD19 CAR-T cells do not work as well against them. They can even cause harm to healthy tissues, instead of targeting the cancer cells. Two studies tried using CTL019 cells on a 43-year-old patient who had already tried 9 other treatments, and they saw some remission with minimal side effects. Hence, researchers are working on finding new targets for tumor cells that are specific to the cancer to eliminate its harmful impact on healthy tissues [6].

3. EFFICACY AND SAFETY

CAR-T cells are showing great promise as a treatment for blood cancers, with long-term data showing that they are effective and have relatively low levels of side effects [11]. The strong remission rates for B-cell lymphoma patients treated with CD19-targeted CAR-T cells show that this type of therapy has the potential to cure patients with cancers that failed to respond to chemotherapy [12]. CAR-T cells can also serve as an important bridge to allogeneic HSCT in patients with B-ALL and can provide prolonged treatment-free remission for patients with MM.

Numerous promising areas of investigation have the potential to improve the durability of remission after this therapy [13].

The use of CAR-T cells to treat blood cancers is growing quickly. These cells are approved to treat B-cell lymphoma, B-cell acute lymphoblastic leukemia, and multiple myeloma that hasn't responded to other treatments. CAR-T cells could become an important treatment for these cancers. Long-term follow-up data shows that CD19-targeted CAR-T cells can potentially cure some patients with B-cell lymphomas [14]. These results suggest that CAR-T cells might need to be combined with stem cell transplants to increase the chances of long-term remission for patients with B-cell acute lymphoblastic leukemia [15,16]. CAR-T cells targeting B-cell maturation antigen have been shown to cause long-lasting remissions in patients with multiple myeloma who have relapsed or are not responding to other treatments. However, it is still unknown if any of these remissions will lead to a cure [13].

4. MECHANISM OF CAR-T CELL THERAPY

CAR-T cell therapy uses an adoptive cell therapy (ACT) approach in which cancer cells are killed using modified T-cells collected from the patient where the process is autologous or taken from a healthy donor where it becomes allogeneic [17,18]. The therapy begins with a specialized process, known as Leukapheresis, whereby white blood cells are extracted from the peripheral blood [10]. Leukapheresis separates mononuclear CD3+ T-cells derived from the bone marrow. This is a 2- to 3-hour outpatient procedure requiring a single collection to obtain a sufficient quantity of the cells [19]. In pediatric patients, due to a more minor total blood volume, susceptibility to hypothermia, hypocalcemia during the procedure, and issues with gaining vein access, a slower rate is used for leukapheresis as compared to adults [20]. A study by McGuirk in the synthesis of CTL019 (tisagenlecleucel), suggests the use of temporary or permanent dialysis-grade catheters for the process [10].

The T-cells collected are cryopreserved and sent to a laboratory for modification. Through a viral vector, usually lentivirus or rotavirus, CAR genes are introduced into T-cells, a process known as transduction [21]. A newer method for transduction where Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/CRISPR-associated (Cas) serve as a means to modify the human genome is also being used. T-cells that are selected are then stimulated within a conducive environment using IL-2 or anti-CD3 antibodies to encourage their growth in a process known as expansion [9].

To ensure the efficacy of therapy and subsequent lasting periods of remission, the patient then undergoes lymphodepletion. The lymphodepletion regimen consists of the administration of cyclophosphamide, 60 mg/kg given for 2 days, and 25 mg/m^2 of fludarabine for 5 days before the CAR-T cell therapy [22]. The regimen through mechanisms such as the removal of reservoirs for homeostatic cytokines like interleukin-2 (IL-2), IL-7, and IL-15, the elimination of immune-suppressive components such as regulatory T cells and myeloid-derived suppressor cells, the initiation of costimulatory molecules, the reduction of indoleamine 2,3-dioxygenase expression in tumor cells, and the enhancement of expansion, function, and enduring presence of infused T cells leads to lymphodepletion.

The CAR-T cell therapy is then introduced to the patient’s bloodstream via a central line. The patients are required to stay proximal to the treatment site for 21-28 days for monitoring against adverse reactions [10,23]. The modified cell in the body leads to cell death of the cancer cells by attachment to expressed antigens. [24] Studies show that this attachment is via three axes such as cytokine secretion causing sensitization of stroma, Fas and FasL axis targets the antigen-negative fraction of tumor cells and the Perforin and Granzyme axis led lysis of the antigen-positive tumor cells.

4.1 Recent Clinical Trials of Car T-Cell Immunotherapy

This table provides an overview of multiple clinical trials testing different CAR T-cell and NK cell therapies for various cancers. The trials span early (Phase I) to mid (Phase II) stages, with a primary focus on safety, efficacy, and treatment outcomes such as remission rates, progression-free survival, and overall survival. Many of the therapies are aimed at treating relapsed or refractory cases of cancers like B-cell malignancies, acute lymphoblastic leukemia, and pancreatic cancer. Common key outcomes across the trials include the incidence of adverse effects, durability of response, and pharmacokinetic evaluations. Several trials also

Table 1. The recent clinical trials of Car T-cell Chemotherapy

Clinical trial Id	Phase	condition targeted	type of car t cell	key outcomes
NCT03919240	I/II	Refractory or Relapsed (R/R) B-Cell Acute Lymphoblastic Leukemia (ALL)	ssCART-19	• Complete remission and overall survival •
NCT04245839	II	Relapsed or Refractory Indolent B-Cell Non-Hodgkin Lymphoma	C-19	• 3 months of therapy for complete response. • • Duration of response was between 12-18 months •
NCT05779917	I	Pancreatic Cancer	Mesothelin/GPC3/ GUCY2C-CAR-T Cells	• Number of patients with dose-limiting toxicity. • • percentage of patients with partial or complete remission (Objective response rate, ORR) •
NCT06420076	I	CD5/CD7 positive T-cell ALL and LBL	CD5/CD7 CAR-T	• Incidence of adverse effects after infusion of therapy • • Disease response to T-cell therapy •
NCT05963100	I/II	Mesothelin (MSLN) positive Ovarian Cancer	TCR-like CAR-T	• Patients OSR • • ORR • • Progression-free survival •

Clinical trial Id	Phase	condition targeted	type of car t cell	key outcomes
NCT05588440	I/II	R/R B-Cell Malignancies	ONCT-88	• Partial or Complete remission • • Evaluate pharmacokinetics of ONCT-808 •
NCT04880434	II	R/R Mantle Cell Lymphoma	**KTE-X19**	• Durable remissions in patients • • Progression free survival. • • Toxicity profile similar to other CAR-T therapies •
NCT06307054	I	R/R Acute Myeloid Lymphoma (AML)	CLL-1 CAR NK cells	• Safety and Efficacy profile of therapy •
NCT04847466	II	Gastroesophageal Junction (GEJ) Cancers Advanced HNSCC	PD-L1 CAR-NK	• Progressionfree survival • • Favorable clinical response rate •
NCT05941156	II	R/R NK/T cell lymphoma /NK cell leukemia	Anti-CD56-CAR T cells	• Safety and efficacy of novel Anti-CD56-CAR T cell therapy •

track objective response rates (partial or complete remission) and the overall safety profile of these therapies. The table reflects the ongoing exploration of CAR T-cell therapy's potential in treating difficult-to-treat cancers, with promising results being reported in terms of remission and survival, albeit with a continued focus on managing adverse effects [25].

5. COST AND ACCESSIBILITY OF CAR T-CELL IMMUNOTHERAPY

CAR T-cell therapy represents a groundbreaking advance in treating hematological malignancies but significant challenges must be overcome to ensure equitable access and inclusivity. The current distribution of facilities offering CAR T-cell therapy is limited, creating geographic and logistical barriers for many patients [26]. Due to the specialized skills required for CAR T-cell collection and administration, clinical trials are often confined to specialized institutes. This necessitates that patients travel or temporarily relocate, [27] often for a minimum of four weeks, causing disruptions in their daily lives and imposing additional burdens such as childcare and work interruptions [28]. This is particularly challenging for patients from lower socioeconomic backgrounds, who may struggle with transportation and other related costs.

5.1 Disparities in Clinical Trial Participation

Despite the growing availability and adoption of CAR T-cell therapy, significant disparities exist in access for minority populations, particularly black patients who are disproportionately affected by multiple myeloma [29]. Factors contributing to unequal access include high costs, transportation difficulties, lower referral rates, geographical limitations, ineligibility due to existing comorbidities, lack of insurance coverage, and insufficient caregiver support. These obstacles are often rooted in racial and socioeconomic inequities [30,3].

Research has shown that cancer patients from racial and ethnic minorities are significantly underrepresented in clinical trials for CAR T-cell therapy. Black patients, in particular, are less likely to receive CAR T-cell therapy for conditions like B-cell lymphoma, multiple myeloma, and acute lymphoblastic leukemia (ALL) [31]. Additionally, both Black and Hispanic patients are underrepresented in clinical trials for CAR T-cell therapies [3]. A study from 2018 to 2022 highlighted this disparity, showing that while minority patients accounted for a substantial percentage of those treated for large B-cell lymphoma (LBCL), their representation among CAR T-cell therapy recipients was notably lower [31]. Research has shown that black patients are less likely to receive CAR T-cell therapy for conditions like B-cell lymphoma, multiple myeloma, and acute lymphoblastic leukemia (ALL) [32,33].

5.2 Geographic Barriers and Socioeconomic Factors

Geographic limitations significantly contribute to disparities in access to CAR T-cell therapy. For instance, in states with the highest percentage of black residents, there are often few or no clinical trial openings for CAR T-cell therapies. This geographic gap means that less than half of black patients live in a county with ongoing clinical trials, limiting their access to these life-saving treatments [34].

Studies have found that patients who receive CAR T-cell therapy in the United States are more likely to be white and reside in urban areas [35]. However, race and ethnicity do not affect the efficacy or neurotoxicity outcomes of CAR T-cell therapy [36]. Some studies even suggest that black patients with multiple myeloma may experience better outcomes than their counterparts when provided with equal treatment [37]. Therefore, it is crucial to enhance CAR T-cell treatment rates among black patients with multiple myeloma in both clinical trials and real-world settings to ensure equitable access.

Internationally, the accessibility of CAR T-cell therapy varies widely. In regions such as Europe and parts of the Asia-Pacific, CAR T-cell therapy is widely used. However, significant disparities persist, with Western European countries generally having better access compared to Central and Eastern European nations [38]. Similarly, in the Asia-Pacific region, countries like Australia, Japan, South Korea, China, and Singapore have implemented "off-the-shelf" CAR T-cell therapies while access remains limited in other parts of the region. Latin America faces similar challenges, with Brazil being the only country with multiple approved CAR T-cell therapies, while access is constrained in other countries like Mexico and Argentina [39].

Africa currently lacks approved CAR T-cell therapy products, facing significant barriers such as limited healthcare resources, infrastructure, funding, and legislative support. The region's focus on combating high disease burdens, such as human immunodeficiency virus (HIV), tuberculosis, and malaria, detracts from resources allocated to developing advanced therapies like CAR T-cell therapy. Additionally, cultural beliefs and traditions influence healthcare decisions, adding complexity to the accessibility of advanced therapies in Africa [40].

5.3 Cost-Effectiveness Analysis

Cost-effectiveness analyses of CAR T-cell therapy are difficult due to the lack of comparable data and uncertainties in clinical evidence [41]. The therapy's approval was based on single-arm, small-scale studies, making it challenging to evaluate its benefits compared to other treatments. Despite these challenges, studies have shown that CAR T-cell therapy is more cost-effective than conventional chemotherapy for patients with relapsed B-cell lymphoma [42]. The therapy has been associated with a higher quality-adjusted life year (QALY), with values ranging from $58,000 to $289,000/QALY [42]. However, the overall cost per QALY affects the willingness to pay (WTP) threshold, which is not always favorable for CAR T-cell therapy.

5.4 Strategies to Improve Cost-Effectiveness and Accessibility

To reduce uncertainty in determining the cost-efficiency of CAR T-cell therapy, longer-term follow-up studies with larger participant groups and comprehensive safety and effectiveness data are necessary. Additionally, reducing the incidence of CRS, a significant side effect of CAR T-cell therapy, is crucial. CRS can be life-threatening and lead to multiple organ dysfunction, increasing treatment costs and complexity [43,44].

Several issues impede global accessibility to CAR T-cell therapy, including affordability, insurance coverage, pricing, and reimbursement [15,16]. The list pricing for FDA-approved CAR T-cell therapies, such as Kymriah®, Yescarta®, Tecartus®, Breyanzi®, and Abecma®, ranges from $373,000 to $475,000 per infusion [20]. Total costs can exceed $1 million per patient when including leukapheresis, lymphodepletion, product infusion, patient management, and side effect monitoring. Improving accessibility requires concerted efforts in pricing policy, regulations, insurance coverage, affordability, and manufacturing operations [45,46].

6. LIMITED APPLICABILITY

CAR-T cell therapy has been successful in the treatment of a range of hematological cancers such as Acute Lymphoblastic Leukaemia, B-cell Lymphoma, etc. but there remains limited efficacy in the management of solid tumors which take up a bulk of cancer cases. One of the reasons for this is due to the expression of antigens on normal cells in varying levels which gives rise to a reduction in specificity to target antigen [47].

Another limitation is the lack of guarantee for durable response despite significant results in remission of patients. The extensive nature of the therapy process from leukapheresis to administration of modified cells, can lead to therapy delay. Since the therapy is relatively new, adequate long-term data on efficacy and toxicity is low and requires further research over extensive periods.

7. FUTURE IMPLICATIONS OF CAR T-CELL IMMUNOTHERAPY

CAR-T-cell therapy is quite successful and in certain cases has been shown to result in long-term remission. Nonetheless, CAR-T-cell treatment is ineffective for certain patients. After receiving CAR-T-cell therapy, relapses typically happen within six months of starting treatment, while late relapses have also been documented [16,48]. According to Cheng et al. [10], the two main ways that resistance to CAR-T-cell therapy can develop are (1) deletion of the CD 19 antigen and (2) TME suppression of CAR-T-cell function. One of the main problems with CAR-T cell treatment is antigen loss. It happens when patients who relapse after treatment have their target antigen removed by CAR-T cells. There are several possible causes for this loss, including CAR-T cell selection or target antigen alterations. To get around this, scientists are looking into methods, like sequential CAR-T cell therapy, which targets several antigens at once [49]. One factor contributing to CAR-T cell resistance is the tumor microenvironment (TME). T-cell exhaustion can be caused by immune checkpoint factors such as PD-1 in the TME, which can impact the efficacy of CAR-T cells. To mitigate this impact and enhance the results of

CAR-T treatment, immune checkpoint inhibitors are being researched [50].

Despite challenges related to cost and accessibility, ongoing research and healthcare policy efforts can lead to more equitable access to CAR T-cell therapy. The healthcare community needs to work collaboratively to address these issues and ensure that this revolutionary therapy benefits a wider range of patients.

8. DISCUSSION

CAR T-cell therapy has demonstrated remarkable efficacy in treating hematological malignancies, yet its high cost and limited accessibility pose significant challenges. To enhance affordability and accessibility, several strategies can be implemented. Decentralizing manufacturing to point-of-care facilities at academic centers can save time and improve logistical efficiency, although this requires substantial infrastructure and training. Advancing manufacturing processes, such as faster techniques and developing allogeneic [34] CAR T-cell products, can reduce costs and improve scalability. Financial assistance programs can help mitigate the high costs, covering treatment, travel, and post-infusion care expenses. Improving insurance coverage and developing comprehensive reimbursement models can ensure more patients can afford the therapy. Increasing the number of medical centers involved in geographically diverse clinical trials and addressing transportation barriers can enhance trial participation rates [37]. Health equity is a complex, multifaceted challenge. Organizations must consider each community's demographics, culture, history of racism, and local events that might influence healthcare-seeking behavior. The long-term goal is to make CAR T-cell therapies available to everyone, across all healthcare barriers. This will require international networking, collaborations, and global partnerships involving both public and private sectors.

Enhancing diversity, equity, and inclusion (DEI) in clinical trials through targeted outreach and support can ensure better access for minority populations [51]. Collaborative partnerships and international networking can facilitate knowledge sharing, resource pooling, and standardized protocol development, improving global availability and quality. National programs and pharmaceutical companies need to support patients by providing financial infrastructure to offset costs and diminish logistical burdens [51]. Policy advocacy for cost reduction, pricing transparency, and expanded health insurance coverage is crucial, as is public health advocacy to raise awareness about the therapy and its benefits. By implementing these strategies, the healthcare community can work towards making CAR T-cell therapy more affordable and accessible, ensuring its life-saving potential is realized for a wider range of patients.

9. CONCLUSION

This study discussed and presented the current literature on CAR T-cell therapy exploring its accessibility, efficacy, and safety. CAR T-cell therapy has emerged as a transformative treatment for hematological malignancies, demonstrating high efficacy and showing promise in clinical applications. Despite the challenges and limitations, the therapy's future holds great potential through ongoing research and innovative solutions. The effectiveness and safety of CAR T-cell therapy have been well-established, offering new hope for patients with limited treatment options. However, addressing challenges such as cytokine release syndrome, target antigen loss, limited applicability, cost, and accessibility is crucial for the therapy's continuous advancement. As research continues to evolve, CAR T-cell therapy is poised to expand its applications to a broader spectrum of cancers, including solid tumors. By implementing strategies to improve DEI, reducing costs, and fostering international collaborations, the healthcare community can work towards making CAR T-cell therapy universally accessible and beneficial for all.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that generative AI technologies such as Large Language Models, etc have been used during writing or editing of this manuscript. This explanation will include the name, version, model, and source of the generative AI technology and as well as all input prompts provided to the generative AI technology.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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